

[54] MANUFACTURE OF  
N-(BENZENESULFONYL)-5-O-DESOSAMI-  
NYL-ERYTHROMYCILAMINE  
DERIVATIVES

[75] Inventors: Gorjana Radobolja; Zrinka  
Tamburasev; Slobodan Djokic, all of  
Zagreb, Yugoslavia

[73] Assignee: Pliva, Pharmaceutical and Chemical  
Works, Zagreb, Yugoslavia

[22] Filed: Jan. 10, 1975

[21] Appl. No.: 540,151

[30] Foreign Application Priority Data

Jan. 14, 1974 Yugoslavia..... 97/74

[52] U.S. Cl. .... 260/210 E; 424/180

[51] Int. Cl.<sup>2</sup>..... C07H 15/22

[58] Field of Search ..... 260/210 E

[56] References Cited

FOREIGN PATENTS OR APPLICATIONS

1,100,267 1/1968 United Kingdom ..... 260/210 E

Primary Examiner—Johnnie R. Brown  
Attorney, Agent, or Firm—Kurt Kelman

[57] ABSTRACT

N-(4-R<sup>2</sup>-benzenesulfonyl)-5-O-desosaminyl-  
erythromycilamine, wherein R<sup>2</sup> is a C<sub>1</sub>-C<sub>5</sub> alkyl radi-  
cal, halogen or NH<sub>2</sub>. The compounds possess antibac-  
terial activity.

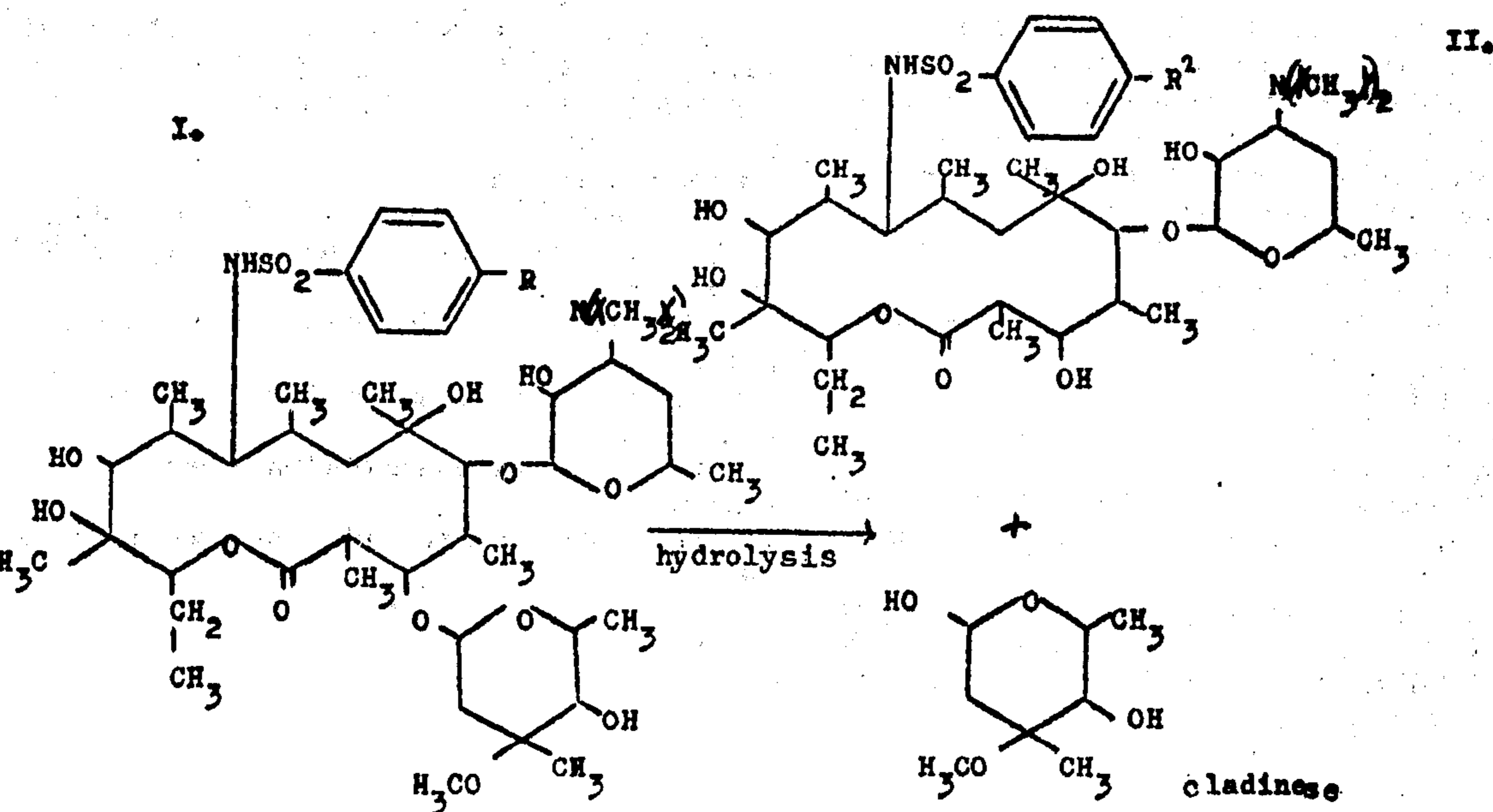
5 Claims, No Drawings

# MANUFACTURE OF N-(BENZENESULFONYL)-5-O-DESOSAMINYL- ERYTHROMYCILAMINE DERIVATIVES

This invention relates to the manufacture of N-(4-benzenesulfonyl)-5-O-desosaminyl-erythromycin derivatives from N-(4-R-benzenesulfonyl)-erythromycin by reaction with diluted mineral acids.

According to the invention, there is disclosed a process for the manufacture of novel N-(4-R<sup>2</sup>-benzenesulfonyl)-5-O-desosaminyl-erythromycin derivatives of the formula II, wherein R<sup>2</sup> is a C<sub>1</sub>-C<sub>5</sub> alkyl radical, halogen or NH<sub>2</sub>, which comprises reacting a compound of the formula I, wherein R is a C<sub>1</sub>-C<sub>5</sub> alkyl radical, halogen or NHCOR<sup>1</sup> (R<sup>1</sup> being C<sub>1</sub>-C<sub>5</sub> alkyl or phenyl), with diluted mineral acids in a convenient solvent (e.g. dimethylformamide, methanol) at room temperature.

The products may be isolated from the reaction mixture by such methods as extraction or crystallisation.



Preliminary bacteriological tests with the novel compounds obtained according to the invention showed that they have an activity on some pathogenic microorganisms as well as a synergistic activity with trimethoprim (Table I).

TABLE I

Compound	MIC in mcg/ml of the tested compounds		
	E.coli 7920	E.coli 8141	Strept.haem.
DEASBr	250	500	62.2
DEASBr			
+	62.2	62.2	0.9
T			
DEASCl	250	250	125
DEASCl			
+	62.2	31.1	7.8
T			
DEASNH <sub>2</sub>	125	125	62.2
DEASNH <sub>2</sub>			
+	62.2	31.1	3.9
T			
DEAST	125	125	62.2
DEAST			
+	62.2	31.1	3.9
T			

DEASBr = N-(4-bromo-benzenesulfonyl)-5-O-desosaminyl EA  
 DEASCl = N-(4-chloro-benzenesulfonyl)-5-O-desosaminyl EA  
 DEASNH<sub>2</sub> = N-(4-amino-benzenesulfonyl)-5-O-desosaminyl EA  
 DEAST = N-(4-methyl-benzenesulfonyl)-5-O-desosaminyl EA  
 EA = erythromycin  
 T = trimethoprim

Since it is known that compounds of the class of erythromycins without the sugar cladinose have no antibacterial activity, but the compounds according to the invention have such an activity, being the hydrolysis products of parent substances in an acidic medium, so their activity and the activity of the parent substances in vitro may have a special meaning for their effect in vivo.

The invention is illustrated by the following Examples:

## EXAMPLE 1

## N-(4-chloro-benzenesulfonyl)-5-O-desosaminyl-erythromycin

N-(4-chloro-benzenesulfonyl)-erythromycin (3 g., 0.0033 moles) was dissolved in 1% methanolic HCl (300 ml.) and left at room temperature for 24 hours. The solution was subsequently evaporated in vacuo.

The residue was dissolved in chloroform (8 ml.) and gradually added drop by drop under vigorous stirring to a mixture of saturated NaCl solution (12 ml.), 20% Na<sub>2</sub>CO<sub>3</sub> solution (20 ml.) and saturated NaHCO<sub>3</sub> solution (12 ml.). After the separation of the layers, the aqueous layer was extracted with chloroform (3 × 10 ml.). The combined chloroform extracts were washed successively with a saturated NaHCO<sub>3</sub> solution (10 ml.) and saturated NaCl solution (10 ml.) and dried over K<sub>2</sub>CO<sub>3</sub>. After the elimination of chloroform, the residue was three times crystallized from chloroform petroleum ether, m.p. 148°-152°C.

Analysis for C<sub>35</sub>H<sub>59</sub>ClN<sub>2</sub>O<sub>11</sub>S. calc.: C 55.94%; H 7.91%; N 3.72%; S 4.26%. obt.: C 55.74%; H 8.14%; N 3.90%; S 4.10%. (M<sup>+</sup>) = 750. [α]<sub>D</sub><sup>20</sup> = -22.55° (1% solution in CHCl<sub>3</sub>)

## EXAMPLE 2

## N-(4-methyl-benzenesulfonyl)-5-O-desosaminyl-erythromycin

N-(4-methyl-benzenesulfonyl)-erythromycin (3 g., 0.0034 moles) in 1% methanolic HCl (300 ml.) was left for 24 hours at room temperature. The solution was then evaporated in vacuo and the residue dissolved in chloroform (8 ml.). The chloroform solution was

added drop by drop under vigorous stirring to a mixture of saturated NaCl solution (12 ml.), 20% Na<sub>2</sub>CO<sub>3</sub> solution (20 ml.) and saturated NaHCO<sub>3</sub> solution (12 ml.). After vigorous stirring the layers were separated and the aqueous layer extracted with chloroform (3 × 10 ml.). the combined chloroform extracts were washed successively with a saturated NaHCO<sub>3</sub> solution (10 ml.) and saturated NaCl solution (10 ml.) and dried over K<sub>2</sub>CO<sub>3</sub>. After the elimination of chloroform, the residue was crystallised 3 times from chloroform/petroleum ether, m.p. 141°-145°C.

Analysis for C<sub>36</sub>H<sub>62</sub>N<sub>2</sub>O<sub>11</sub>S. calc.: C 59.15%; H 8.55%; N 3.83%; S 4.38%. obt.: C 59.21%; H 8.79%; N 4.00%; S 4.51%. (M<sup>+</sup>) = 730. [α]<sub>D</sub><sup>20</sup> = -9.04° (1% solution in CHCl<sub>3</sub>).

### EXAMPLE 3

#### N-(4-bromo-benzenesulfonyl)-5-O-desosaminyl-erythromycin

N-(4-bromo-benzenesulfonyl)-erythromycin (3 g., 0.0031 moles) was dissolved in 1% methanolic HCl (300 ml.) and then left for 24 hours at room temperature. The solution was then evaporated in vacuo. The residue was dissolved in chloroform (8 ml.) and gradually added drop by drop under vigorous stirring to a mixture of saturated NaCl solution (12 ml.), 20% Na<sub>2</sub>CO<sub>3</sub> solution (20 ml.) and saturated NaHCO<sub>3</sub> solution (12 ml.). After separating the layers, the aqueous layer was extracted with chloroform (3 × 10 ml.). The combined chloroform extracts were washed successively with a saturated NaHCO<sub>3</sub> solution (10 ml.) and a saturated NaCl solution (10 ml.) and dried over K<sub>2</sub>CO<sub>3</sub>. After the elimination of chloroform, the residue was crystallised 3 times from chloroform/petroleum ether, m.p. 151°-154°C.

Analysis for C<sub>35</sub>H<sub>59</sub>BrN<sub>2</sub>O<sub>11</sub>S. calc.: C 52.82%; H 7.47%; N 3.52%; S 4.03%. obt.: C 52.76%; H 7.71%; N 3.30%; S 4.07%. (M<sup>+</sup>) = 794 [α]<sub>D</sub><sup>20</sup> = -23.78° (1% solution in CHCl<sub>3</sub>)

### EXAMPLE 4

#### N-(4-amino-benzenesulfonyl)-5-O-desosaminyl-erythromycin

N-(4-acetylamino-benzenesulfonyl)-erythromycin (3 g., 0.0032 moles) was dissolved in 1% methanolic HCl (300 ml.) and left for 24 hours at room temperature. The solution was then evaporated in vacuo. The residue was dissolved in chloroform (12 ml.) and added drop by drop under vigorous stirring to a mixture of saturated NaCl solution (12 ml.), 20% Na<sub>2</sub>CO<sub>3</sub> solution (20 ml.) and saturated NaHCO<sub>3</sub> solution (12 ml.). After separating the layers, the aqueous layer was extracted with chloroform (3 × 10 ml.). The combined chloroform extracts were washed successively with a saturated NaHCO<sub>3</sub> solution (10 ml.) and a saturated NaCl solution (10 ml.) and dried over K<sub>2</sub>CO<sub>3</sub>. After the elimination of chloroform in vacuo, the residue was crystallised 3 times from chloroform/petroleum ether, m.p. 165°-169°C.

Analysis for C<sub>35</sub>H<sub>61</sub>N<sub>3</sub>O<sub>11</sub>S. calc.: C 57.43%; H 8.40%; N 5.74%; S 4.38%. obt.: C 56.52%; H 7.85%; N 5.00%; S 3.70%. (M<sup>+</sup>) = 731. [α]<sub>D</sub><sup>20</sup> = -10.98° (1% solution in CHCl<sub>3</sub>).

What we claimed is:

1. An N-(4-R<sup>2</sup>-benzenesulfonyl)-5-O-desosaminyl-erythromycin, wherein R<sup>2</sup> is a C<sub>1</sub>-C<sub>5</sub> alkyl radical, halogen or NH<sub>2</sub>.
2. The erythromycin of claim 1, wherein R<sup>2</sup> is methyl.
3. The erythromycin of claim 1, wherein R<sup>2</sup> is bromine.
4. The erythromycin of claim 1, wherein R<sup>2</sup> is chlorine.
5. The erythromycin of claim 1, wherein R<sup>2</sup> is NH<sub>2</sub>.

\* \* \* \* \*